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AN EARLY STAGE OF AN EXPERIMENTALLY PRODUCED EXTRAUTERINE PREGNANCY AND THE SPONTANEOUS PARTHENOGENESIS OF THE EGGS IN THE OVARY OF THE GUINEA PIG.[1]

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The observation on which I wish to report is of great interest from several points of view. It explains the negative result of our former attempts which aimed at producing experimentally an extrauterine pregnancy in the guinea pig. It contributes to the understanding of the mechanism of the sexual cycle and it makes certain my previous conclusions, which formerly had only been probable, concerning the fargoing parthenogenetic development of ova in the ovary of the guinea pig, conclusions which our previous studies had made very probable. In a great number of previous experiments we made incisions in various parts of the uterus of the guinea pig and at different times after copulation.[2] Under these circumstances it certainly must often have happened that fertilized eggs left the uterine cavity. But extrauterine pregnancy did in no case take place under such circumstances. Even after ligation of the fallopian tubes we were not able to observe the occurrence of an extrauterine pregnancy. This latter observation is in accordance with some experiments of Mandl and Schmidt.[3] It was of interest to determine what was the fate of the ova which left the lumen of the uterus and passed into the peritoneal cavity after fertilization. An observation

[1] From the pathological laboratory of the Barnard Free Skin and Cancer Hospital, St. Louis.

[2] Leo Loeb and John W. Hunter, *University of Pennsylvania Medical Bulletin*, Dec., 1908.

[3] *Archiv f. Gynaecol.*, 56, 1898.

which we made in the course of our continued experiments serves to clear up this point.

Two days, sixteen hours after copulation, incisions were made into the uterus of a guinea pig. The weight of the animal at the time of the operation was 550 grams. The incisions were longitudinal and extended through both horns of the uterus up to near the point of juncture with the tubes. Besides the longitudinal incisions a number of transverse incisions into the uterine wall were made. Eighteen days after copulation uterus as well as one of the ovaries was taken out for examination. The ovary was cut into serial sections. Small follicles in the early stages of development, as well as other follicles in early stages of connective tissue atresia were found. In addition there were many follicles in the last stages of follicular atresia. There were also present several young corpora lutea, the center of which was partly filled out by connective tissue, while the center of the cavity had not yet been organized by connective tissue. There were furthermore present corpora lutea in an early stage of retrogression, as well as yellow bodies, completely atretic corpora lutea. These findings correspond to an ovary about three days after ovulation.

Microscopic examination of those parts of the uterus which had not been incised during the operation showed cylindrical surface and glandular epithelium with numerous mitoses in the glandular ducts. The fundi of the glands are somewhat smaller. In the lumen of the uterus there are some polynuclear leucocytes, a greater number of which are found in the ducts of the glands. In the connective tissue of the mucosa as well as in the surface epithelium the presence of several small round cells is noted. There are very few mitoses in the connective tissue of the mucosa which is rich in nuclei. These findings correspond to a condition of the uterus about 3–3½ days after copulation.

Near the tubal end of one of the uterine horns, not far from the usual situation of the ovary there was a small nodule. This nodule was cut in serial sections, and its structure is best explained by referring to the illustrations.

Fig. 1 shows the position of the embryo.

(*a*) It lies in the neighborhood of the fallopian tube.

(*b*) Some distance from the embryo we see the cut wall of the uterus.

(*c*) In the direction towards the tube we see the musculature of the uterus, in the opposite direction the epithelium with the

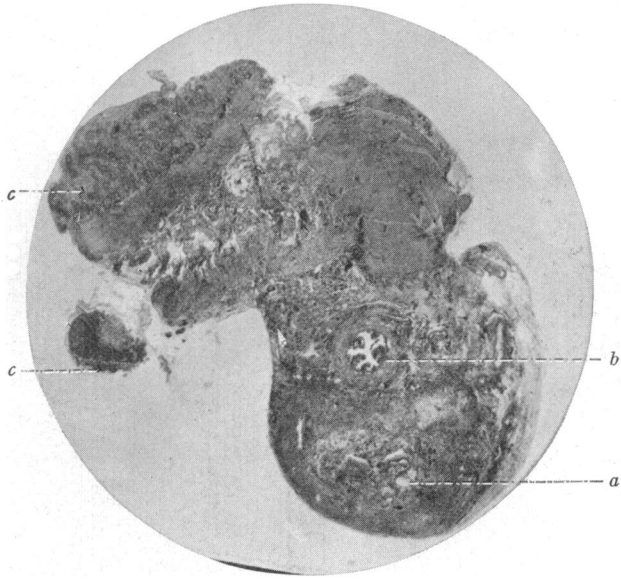

FIG. 1. Low power. *a*, embryo; *b*, Fallopian tubes; *c*, everted walls of the uterus.

A more detailed explanation of the figures is found in the text.

FIGS. 1, 2, 3, 4 and 6 are from microphotographs. Fig. 5 from a drawing.

glands and the connective tissue is visible. In the detached part of *c* the glands have the character of mucous glands. At this place the mucosa of the uterus is everted as a result of the incision. If we follow on further sections the position of the placenta which surrounds the embryo proper, we find that at some distance from the embryo proper it dips into the peritoneal side of the uterus at a place above the beginning of the incisions, where therefore the uterine lumen is still intact, and it even penetrates into a fissure of the musculature of the uterus. Further downwards the embryonal placenta extends to the peritoneal tissues of the upper part of the incised uterus. Fig. 1 of course represents only one section while the description which we just gave is based on a study of a number of serial sections. The egg embedded itself

evidently in the connective tissue between the upper end of the uterus and the lower end of the tube and its derivatives penetrated still deeper between the musculature of the uterus in the direction from the peritoneal side.

The character of the embryonal structures and their relation to the surrounding tissue are more clearly shown on Fig. 2. *b* is

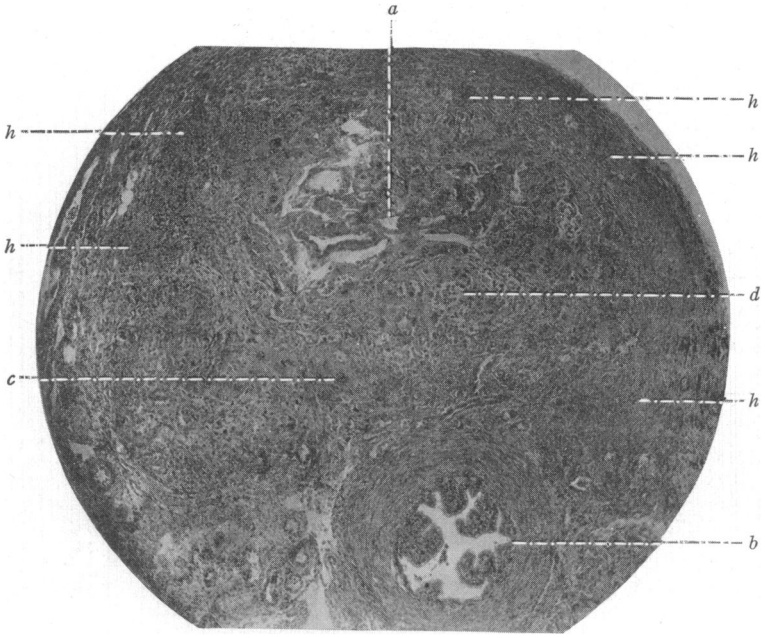

FIG. 2. The developing embryo; somewhat higher magnification. *a*, embryonal structure (neural canal?); *b*, Fallopian tube; *c*, giant cells of the embryonal placenta; *d*, cuboidal cells of the embryonal placenta surrounding cavities; *h*, hemorrhages in the surrounding connective tissue.

the fallopian tube. *a* is the embryo, which is surrounded by placental structures *c* and *d* and other similar not especially designated structures. In the periphery of these structures are found extensive hemorrhages into the connective tissues and these are in turn surrounded by strands of connective tissue and by blood vessels. The entire region between the tubes and the outer hemorrhagic zone is filled out by embryonal placenta.

The embryo proper corresponds to a developing guinea pig at a stage directly following the formation of the germ layers.

A points to a central structure, which probably corresponds to the Anlage of the neural tube. Under the abnormal conditions under which the embryo must develop, the various embryonic structures are evidently somewhat distorted. Fig. 3 shows the

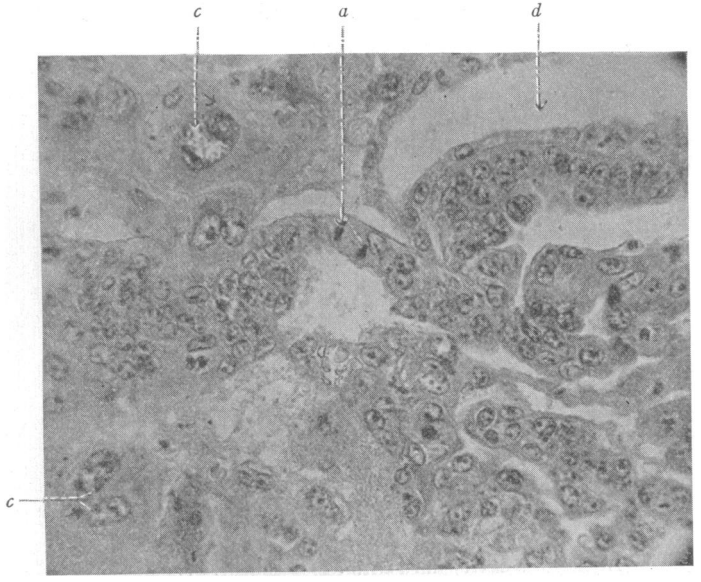

FIG. 3. The embryo proper, higher magnification. *a*, mitosis; *c*, surrounding giant cells; *d*, a structure which perhaps corresponds to the placental cavities lined with cuboidal cells.

central part of the embryo at a higher magnification. *A* points to the same cavity as *a* in Fig. 2. The cell designated by *a* is seen in the process of mitotic division. Other embryonal cells also divide mitotically at various places. Surrounding the central parts of the embryo we find epithelial structures arranged in layers adjoining as is shown on Fig. 2. Giant cells *c* surround the embryo at various places on Fig. 3 in a similar way as seen on Fig. 2. A larger number of giant cells are also found at a somewhat greater distance from the embryo. These giant cells are arranged typically around cavities, which are lined by smaller cuboidal cells. *D* on Fig. 2 points to such a cavity lined with such cuboidal cells. Perhaps also the canal *d* on Fig. 3 corresponds to such a cavity. The small cuboidal cells often proliferate and

their proliferation leads to the formation of papillary excrescences into the cavities. These excrescences fill sometimes a great part of these cavities. Mitoses often appear in these cuboidal cells. Fig. 4 shows such a placental structure at a higher magnification.

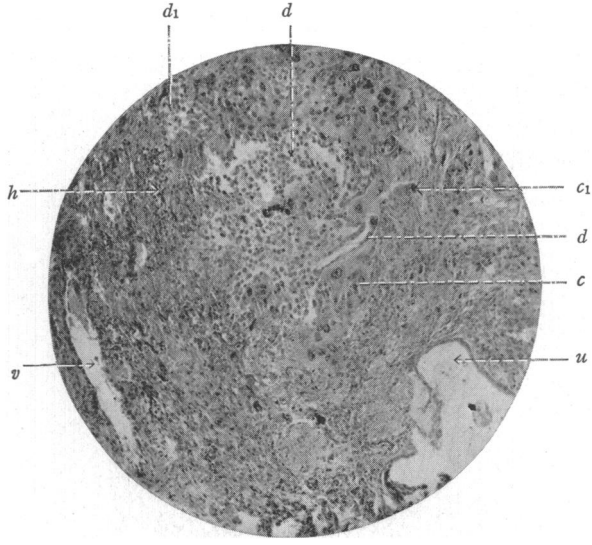

FIG. 4. A placental cavity lined with cuboidal cells. *c*, giant cells; *d*, cuboidal cells lining a cavity and forming papillary excrescences; *c'*, a giant cell penetrating into the surrounding connective tissue; *v*, blood vessels; *h*, hemorrhages in the connective tissue; *u*, experimentally misplaced uterine epithelium.

d points to a cavity lined with cuboidal cells. The cuboidal cells form papillary proliferations into the lumen. The cavity bulges into the surrounding tissue at *d*1. The cavity is surrounded on several sides by giant cells *c* and these giant cells protrude into the cavity and divide it into two parts. These giant cells have the power to penetrate farther into the surrounding tissue independently. *C*1 represents such a giant cell, which penetrates into the surrounding fibrous tissue. Surrounding this placental structure we find connective tissue in which there are many hemorrhages *h*. *U* represents a cavity lined with uterine epithelium. *v* represents a blood vessel. Fig. 5 represents a drawing of a similar placental structure. *D* represents the cavities lined with cuboidal cells, and partly filled with the proliferated cuboidal

cells. *C* are the giant cells surrounding the cuboidal cells. *F* is fibrillary connective tissue in which there are many hemorrhages *h*. There is nowhere a formation of a decidua. *v* is a blood vessel.

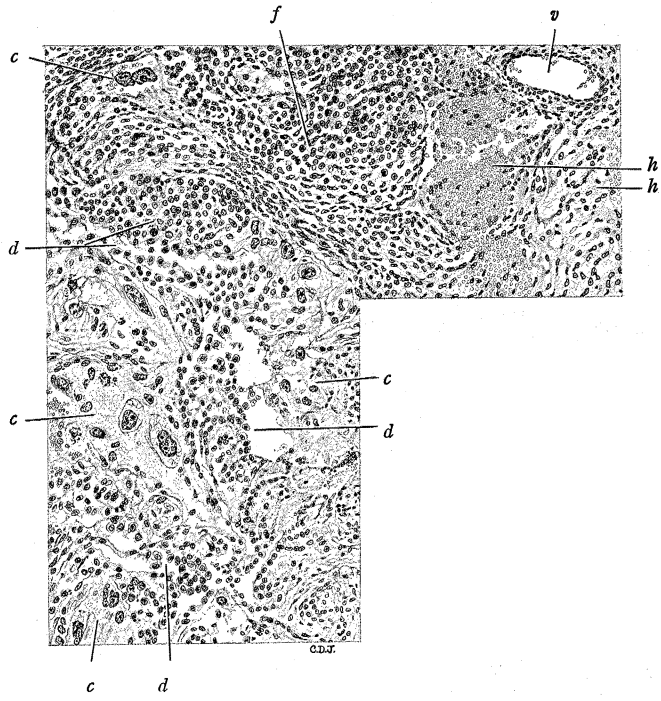

FIG. 5. A typical placental structure. The various letters have the same significance as in Fig. 4.

As we have already seen on Fig. 4, the giant cells penetrate deeper into the tissue, independently of the small cuboidal cells. They prefer especially the neighborhood of blood vessels, penetrate the walls of the latter and replace the endothelial cells. Blood vessels thus changed are of course thereby weakened, and they are no longer as well able to resist to the full extent the blood pressure, and thus hemorrhages into the tissue, as so frequently seen, result. Fig. 6 shows two vessels *v*. Giant cells *c* have advanced up to the lumen of these vessels and substitute the endothelial cells. In *c*1 also there lies a giant cell in the tissue. At many places there are hemorrhages *h* in the connective tissue. In the periphery of the upper half of the section, connective

tissue surrounds the structure. *d* points to a cavity filled with small cuboidal cells.

These findings will have to be interpreted in the following way. At the time when the incisions were made into the uterus, namely two days and sixteen hours after copulation, the ova had probably already left the tube and had reached the upper part of the uterine cavity. At this time one or more of the ova left the uterine cavity through the incision into the uterine wall

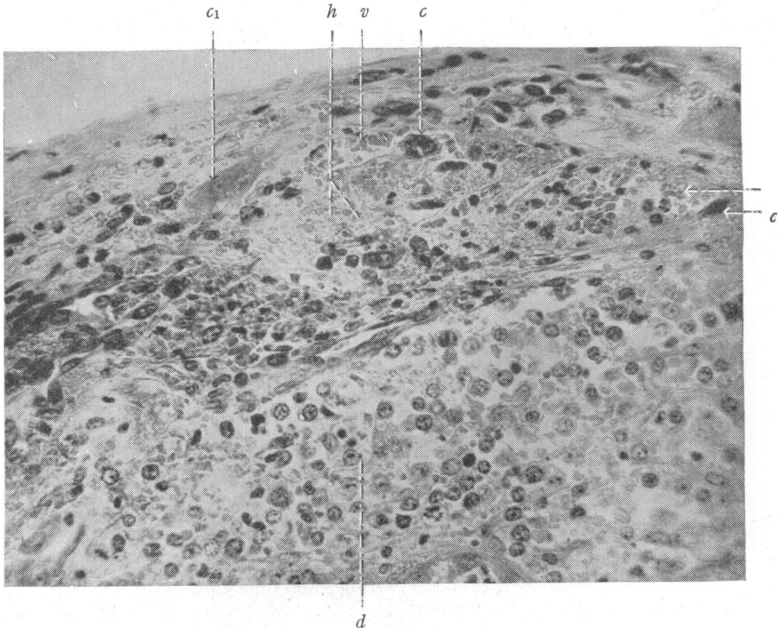

FIG. 6. Placental embryonal giant cells penetrate into the vessel wall. *v*, blood-vessels; *c*, giant cells substitute vascular endothelial cells; *c'*, a giant cell lying in the host tissue; *h*, hemorrhages in the host connective tissue; *d*, cuboidal placental cells of embryonal origin.

and one of the ova passed around the outer side of the upper end of the left uterine horn, and embedded itself in the connective tissue between the tube and the upper end of the left uterine horn. A part of the embryonal placenta in the course of development penetrated farther into the musculature of the uterine horn. The fertilization of this ovum had in accordance with the

general view concerning the time of fertilization of the guinea-pig ovum already taken place at the time of the operation. We excised the nodule fifteen days eight hours after the incisions had been made.

Our description of the embryo clearly shows that under the existing abnormal conditions the development of the ovum was greatly retarded. The embryo is still alive and even growing, as the mitoses, which were found at various places, indicate, but the embryo is found to be at a very much earlier stage of development than one would expect eighteen days after copulation. The embryonal placenta also is only very incompletely developed. While the normal placenta of the guinea pig shows a complicated structure at this period of development, in our case the embryonal placenta consist solely of layers of small cuboidal cells, which usually line cavities, and produce papillary excrescences projecting into the cavities. On the outer side of these cavities there are giant cells. The giant cells penetrate also independently into the surrounding connective tissue and substitute walls of blood vessels, and thus contribute to the hemorrhages which we find so frequently. Cuboidal cells as well as giant cells are growing actively by mitosis—the latter however to a lesser degree. The surrounding host tissue remains passive. The embryonal tissue is surrounded by fibrillar connective tissue containing the ordinary connective tissue cells. *There is nowhere an attempt at the formation of a decidua on the part of the host tissue.*

These observations are in entire accord with our former experimental findings from which we concluded that in the guinea pig solely the connective tissue of the uterine mucosa is able to produce decidua in response to artificial stimuli, as cuts and foreign bodies while the fallopian tube, peritoneal and other connective tissue are unable to do so.[1]

These additional observations again prove the similarity in the mode of action of the artificial stimuli leading to the formation of a decidua on the one hand and of the ovum on the other hand. In a similar manner as the artificial stimuli were not able to call forth a

[1] Leo Loeb, *Zentralblatt für Physiol.*, Bd. XXIII., No. 3; *Journal Am. Med. Association*, Vol. LIII., p. 1471, 1909.

formation of decidua in the peritoneal connective tissue, the ovum is likewise unable to do so.[1]

These observations furthermore clear up the fate of the ovum in cases in which it is not able to develop normally in the uterine wall. Frequently a fixation of the ovum does not take place in such abnormal cases, especially on the smooth peritoneal epithelium. In other cases however the ovum fixes itself and begins to develop in the connective tissue without however finding the necessary decidual reaction on the part of the surrounding connective tissue. In such cases the development of the embryo proper as well as of the embryonal placenta is very much retarded as compared to the normal development; furthermore the embryonal differentiation also remains incomplete and we may assume, that after some time the growth ceases and the embryonal structure is substituted by host connective tissue in a similar manner as in the ovary of the guinea pig. We find therefore in the guinea pig no or only a very much retarded and incomplete development of the ovum outside of the uterus. This is in all probability due to the fact that the host tissue is not suited to receive the ovum and to supply it with the necessary food stuffs. In this case the host tissue behaves passively in contradistinction to the uterine mucosa. This conclusion agrees with the fact that we find a general parallelism in the ability of the uterine mucosa to produce decidua or deciduomata and to permit a normal development of the ovum. As I have previously shown, various experimental interferences, as for instance extirpation of the corpora lutea or of the ovaries, have approximately to the same extent an inhibiting influence on the development of deciduomata and of pregnancy. We may thus conclude that the ability of the host connective tissue to produce a decidua in a normal manner is of significance for the normal development of pregnancy.

We see therefore that in the guinea pig the ovum does either not develop at all outside of the uterus or in case an extrauterine fixation of the ovum should take place, the development is much retarded and soon comes to a standstill. As our present and

[1] As we shall later especially emphasize, the same holds good in the case of the parthenogenetic development of the egg in the ovary of the guinea pig.

especially our previous observations concerning the parthenogenetic pregnancy in the ovary of the guinea pig demonstrate,[1] the development of the embryonal placenta preponderates relatively very much over that of the embryo proper, probably because as I have already suggested, in contact with the host tissue the derivatives of the ovum produce mainly the placental structures. This is very marked in the case of the parthenogenetic development in the ovary of the guinea pig, where in typical cases under those conditions placental structures are found exclusively and only exceptionally the embryo proper begins to develop.

These observations explain apparently very well the fact, that while in the guinea pig a further going development of the ovum is possible *after extrauterine fixation*, in man a complete extrauterine development is not an infrequent occurrence. Our findings suggest as one of the causes for this difference in occurrence of extrauterine pregnancy in man and guinea pig, the fact that in the case of man the host tissue offers a more suitable soil than in the case of guinea pig; while as we saw in the latter the development of the decidua in response to various kinds of stimuli takes only place in the connective tissue of the uterine mucosa, in the case of man the connective tissue of various pelvic organs and even the appendix is able to produce decidua as many observations show. In accordance with this interpretation a number of observers actually reported the development of a decidua in the fallopian tube in cases of tubal pregnancy. It is very probable that in cases of tubal pregnancy in which a decidua was not found in the tube, we had to deal with stages in which the chorionic wandercells had already penetrated deep into the host tissue and thus gradually destroyed the decidua; in a similar manner in the case of the guinea pig it can readily be seen that the wandercells of the embryonal placenta destroy a greater part of the decidua. It is very probable that from a certain stage of embryonal development on, the decidua is no longer indispensable as far as the continued existence and further development of pregnancy are concerned.

[1] *Roux's Archiv*, Bd. XXXII., p. 662, 1911; *Zeitschrift f. Krebsforschung*, 11. Bd., 2. Heft, 1912.

Our observations are also of interest from another point of view. We know that under ordinary circumstances the corpus luteum remains longer preserved in pregnancy than in the non pregnant animal. Pregnancy prolongs the sexual cycle. We may now inquire into the cause of the prolongation of the life of the corpus luteum during pregnancy. Several years ago I pointed out, that the growth of the embryo might perhaps directly or indirectly prolong the life of the corpus luteum during pregnancy.[1]

Now we find in our case a small embryo as well as an embryonal placenta developing outside the uterus. Notwithstanding this fact a new ovulation had taken place about three days previously and accordingly the corpora lutea of the preceding sexual cycle which had been terminated at the time of the last ovulation were degenerated.

This observation proves that a developing embryo including embryonal placenta is in itself not sufficient to protect the corpus luteum from degeneration, and to prevent a new ovulation. It is possible that the maternal placenta is concerned in the prolongation of the life of the corpus luteum either alone or in connection with the embryo, which latter as our further experiments have shown, prolongs noticeably the life of the experimental placentomata (deciduomata). Indeed experiments which I carried out some time ago have shown that the development of deciduomata without the development of an embryo is able to prolong the sexual period; while normally the sexual cycle in the guinea pig has a duration of from 15 to 18 days, it lasts from 20–30 days after production of deciduomata.[2] Whether as a result of these experimental interferences also the life of the corpus luteum is prolonged will have to be still further investigated.

Our observations are furthermore of significance for the interpretation of certain structures, which I found in about 5 per cent. of the ovaries of young guinea pigs.[3]

In as much as these structures become absorbed after a certain time and are substituted by connective tissue, these structures

[1] *Zentralblatt f. Physiol.*, Bd. XXIV., Nr. 6; *Medical Record*, June 25, 1910.

[2] Leo Loeb, BIOLOGICAL BULLETIN, Vol. XXVII., July, 1914.

[3] *Arch. f. mikrosk. Anatomie*, Bd. 65, 1905; *Roux's Archiv*, Bd. XXXII., p. 662, 1911; *Zeitschrift f. Krebsforschung*, 11. Band, 2. Heft, 1912.

must in fact occur more frequently than the direct findings suggest. We have to deal with formations which resemble closely structures of the embryonal placenta, and they originate in ovarian follicles. They are either well preserved or are found in the process of retrogression and in the end are substituted by connective tissue. In two cases I was able to find besides embryonal structures proper, for instance the Anlage of the nervous system. It had been known previously and I myself had described processes which had to be interpreted as the first segmentations of eggs in atretic follicles which in consequence of the abnormal conditions under which they took place followed as might have been expected an abnormal course.[1] The interpretation that we have to deal merely with the disintegration of the ova can be excluded with certainty. Such an interpretation would be contradicted by the regularity of the divisions. Furthermore we may find in these various segments either nuclei or the remnants of nuclear spindles and I was able to observe the simultaneous presence of a mitosis in each one of the two such segments. These segmentations also are found chiefly in the ovaries of the young guinea pigs. A somewhat furthergoing formation of the first segments in ovarian eggs has recently been described in armadillo by Newman.[2]

In all these cases we have merely to deal with the first parthenogenetic segmentations of the ovum, while our observations in the ovary of the guinea pig prove a much furthergoing development leading to the formation of embryonal placenta and of embryos in the stage of the germ layers within the ovary. It is of course natural, as I emphasized on a former occasion, that under these abnormal conditions the processes of development cannot follow an altogether normal course, and it was therefore

[1] Leo Loeb, "On Progressive Changes in the Ova in Mammalian Ovaries, *Journal of Medical Research*, Vol. VI., 1901. *Arch. f. mikrosk. Anat.*, Bd. 65, 1905.

[2] H. H. Newman, BIOLOGICAL BULLETIN, XXV., p. 52, 1913. It may be especially emphasized that our interpretation of the placental and embryonal structures found by us in the ovaries of guinea pigs does in no way depend on the interpretation of those changes in the ova within the ovaries of the guinea pig which in common with previous authors we held to be early abnormal segmentations of ova, while a number of other investigators interpreted them as of a degenerative character. There can be no doubt about the presence of further developed embryonal structures in the ovaries of guinea pigs.

desirable that a confirmation of our interpretation of these ovarian structures should be obtained. The findings which we have just communicated offer the desired confirmation. In our new observations we have also to deal with embryonal structures found in the peritoneal connective tissue and developing in an abnormal situation without being aided by the host tissue through the formation of a decidua. We have of course to consider the fact that in the ovary the limitation of space is still more marked than in the connective tissue on the outer side of the fallopian tube and of the uterus. In both cases the placental structures preponderate over the embryonal ones proper; in both a retardation in the development is found and a preponderance of certain placental structures. Such favored structures are the layers of cuboidal cells, lining cavities, forming papillary excrescences into these cavities and surrounded at the periphery by giant cells which latter penetrate in both cases into the surrounding tissue, especially around the blood vessels, the walls of which they may perforate, thus giving rise to hemorrhages. The identity of both formations, namely of the experimentally produced extrauterine pregnancy which we have just described and of the embryonal structures developing parthenogenetically in the ovary becomes quite evident, when one compares the microscopic sections of both of these formations. The microphotographs and the drawings also show the similarity.

The similarity of the embryonal structures proper becomes clear through a comparison of Figs. 2, 3, and 6 in the former communication (*Zeitschrift für Krebsforschung*),[1] and of Figs. 2 and 3 in the present communication. The similarity of the placental structures is made evident through a comparison of drawings 1, 2 and 4 in the *Archiv f. mikrosk. Anatomie*,[2] of the Figs. 10, 12, 14 and 15 in the *Zeitschrift für Krebsforschung* with Figs. 4 and 5 of the present article. On several of these former figures there were also represented the relations of the wandering giant cells to the blood vessels and the hemorrhages resulting therefrom.

Our new observations render it therefore certain that a fargoing parthenogenetic development of ova takes place in the ovaries of a

[1] *Loc. cit.*

[2] *Loc. cit.*

relatively large number of guinea pigs, leading in the first place to the formation of placental structures, in some cases however also to the formation of embryos in the stage of the germ layers. We have discussed the possible causes for this parthenogenetic development on another occasion.[1] We have perhaps to deal with a development which is caused by changes in the circulation and in the exchange of gases at the time and in consequence of the rupture of follicles.

Such an explanation would be in accordance with the fact that the first segmentations of the ovum in the ovary of the guinea pig are found especially in atretic follicles, that the segmentations set in with beginning atresia and then gradually progress. Now we know that the atresia of follicles is more marked, than at any other time, at the time of ovulation.[2] In this connection it is especially worthy of notice that the first segmentations of the ova in the ovary as well as the furthergoing parthenogenetic development, which leads to the formation of embryonal and placental structures, is preferably found in the ovaries of young animals. The latter, however, occurs occasionally also in somewhat older guinea pigs. In such cases we may perhaps have to deal with structures which originally developed in younger animals, which then however had remained stationary for a longer period of time.

We have still to discuss the significance of these structures for the interpretation of certain pathological formations, namely the embryomata and the chorion epitheliomata of the female germ gland. The large majority of pathologists assume in agreement with the suggestion of Bonnet and Marchand that these pathological structures take their origin from misplaced blastomeres and not from the parthenogenetically developing ovum. As I formerly emphasized[3] our observations make it very probable that such pathological formations originate from parthenogenetically developing ova. They are therefore the "descendants" and not the "brothers" of the organism in which they originate. We may assume that in certain cases the parthenogenetic develop-

[1] Leo Loeb, *Proceedings Am. Philosophical Society*, Vol. L., p. 228, 1911.

[2] Leo Loeb, *Journal of Morphology.*

[3] *Zeitschrift f. Krebsforschung, loc. cit.*

ment of ova leading to these pathological structures begins only after birth. In a similar manner as we saw that embryonal placenta as well as the embryo proper can develop from the parthenogenetically segmenting ovum and that the embryonal placenta can be formed without the simultaneous development of the embryo proper, thus chorion epitheliomata may originate in the ovary without any accompanying embryonal structures proper. In other cases however there develop mainly the embryonal structures proper or certain of their parts.

This conception of these structures explains the fact that they are mainly found in the germ glands. On the other hand, there exists no reason, why we should expect that aberrant blastomeres should mainly be found and develop at this place. Furthermore I have never been able in the many hundreds of ovaries of guinea pigs which I have examined microscopically to find a structure resembling a misplaced blastomere.

We still have to explain why these structures are occasionally also found in the male germ glands and especially, why teratomata occur also, although less frequently, at other parts of the body, outside of the germ glands. As far as their occurrence in male germ glands is concerned, it might be explained by the fact that in a certain number of cases cells of both sexes may be found in the same individual, that therefore true hermaphroditism occurs. That this is not so rare an occurrence as has been assumed has recently been shown by L. Pick.[1] We have perhaps also to consider the possibility that at a certain stage of development also the male germ glands are capable of developing in a similar manner as the ova. However at the present time there exist no facts supporting such an hypothesis.

We know furthermore that in the course of embryonal development the germ cells migrate. It is therefore conceivable that occasionally one of their number may follow a wrong path and thus give origin to the formation of the teratomata outside of germ glands. While we are thus able to explain the origin of these structures on the basis of a parthenogenetic development of ova we do not intend to deny the possibility that under certain conditions irregularities in the embryonal development may lead

[1] Cited from a review in the *Münch. med. Wochenschrift*, 1913.

to the transformation of blastomeres or of remnants of not fully differentiated embryonal tissues into teratomata, an hypothesis which would be in accordance with the finding of misplaced blastomeres by W. Roux in the course of the embryonal development of amphibian eggs.

Summary.

1. It is possible in the case of guinea pigs to produce experimentally the first stages of an extrauterine pregnancy.

2. In a similar manner, as in the case of guinea pigs experimental interferences of various kinds are not able to call forth the production of deciduomata in the connective tissue outside of the uterine mucosa after the discharge into the circulation of the sensitizing substance which is secreted by the corpus luteum, the developing ovum is unable to call forth a decidual reaction.

3. Under the conditions produced by us experimentally the development of the embryo is very much retarded and will in all probability come to a standstill after some time. Neither does the embryonal placenta develop in an entirely normal manner, although quantitatively the embryonal placental structures preponderate considerably over the embryonal proper. It is very probable that the lack of the decidual and of the typical blood vessel reaction on the part of the host connective tissue is the cause of this abnormal development. In man an extrauterine decidua can develop and accordingly here a fully developed extrauterine pregnancy is not rare. As we have shown previously the effect of the extirpation of the corpora lutea on the formation of the decidua and on the development of pregnancy is approximately parallel. This is an additional fact which renders probable the significance of the decidual reaction for the complete development of the extrauterine pregnancy. The decidual reaction is at least one of the conditions which has to be considered in this connection.

4. Notwithstanding the presence of a young, developing embryo in the extrauterine connective tissue a degeneration of the corpora lutea and a new ovulation took place in the ovary. This proves that the persistence of the corpora lutea during pregnancy does not depend upon a substance secreted by the embryo; it is

probable that the growth of the decidua perhaps in combination with the growth of the embryo prolongs directly or indirectly the life of the corpora lutea during pregnancy. Thus far experiments, which we have carried out in order to decide this question, have shown that the presence of living and growing deciduomata prolongs the sexual period; furthermore that pregnancy prolongs the life of the deciduomata. Further investigation will decide whether or not these effects are exerted indirectly by means of the corpus luteum.

5. Our experiments render it certain that the structures which we found in a considerable number of guinea pigs and which we formerly interpreted as early stages of parthenogenetically developed pregnancies in the ovaries of guinea pigs really represent a relatively far going parthenogenetic development of ova which may lead to the formation of embryos in the germ layer stage which however usually leads merely to the formation of an embryonal placenta probably as a response of the developing ovum to the influence exerted by the contact with the surrounding host tissue. We show furthermore the significance these findings have for the interpretation of the teratomata and chorionepitheliomata of the germinal glands.

6. The embryonal wander cells destroy outside as well as within the wall of the uterus bloodvessels of the surrounding host tissue in the ovary as well as in the peritoneal connective tissue and they thus cause hemorrhages in the surrounding host tissue.